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RAWLINGS, STEPHEN L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/929,665	BANDER, NEIL H.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *144,156-168,170-204 and 206-218* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *144,156-168,170-204 and 206-218* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed October 11, 2007, is acknowledged and has been entered. Claim 205 has been canceled. Claims 144, 159, 172, 178, 180, 181, 184, 185, and 204 have been amended. Claims 211-218 have been added.

2. Receipt of the declaration under 37 C.F.R. § 1.131 by Neil H. Bander filed October 11, 2007, is acknowledged.

3. Claims 144, 156-168, 170-204, and 206-218 are pending in the application and are currently subject to examination.

Ownership

4. Applicant's representative has resolved the issue of common ownership, providing a statement at page 15 of the amendment filed J October 11, 2007, that the present application and commonly assigned U.S. Patent No. 7,045,605 B2 were commonly owned at the time the invention in this application was made.

5. As noted in the preceding Office action, claims 144, 156-168, 170-177, 180, 184-203, and 208-210 are directed to an invention not patentably distinct from claims 1-142 of commonly assigned copending Application No. 10/379,838. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in the preceding Office action.

The rejection on the ground of nonstatutory obviousness-type double patenting has been rendered moot by the terminal disclaimer filed February 2, 2007.

Nevertheless, as explained previously, the issue remains as to the inventions were commonly owned *at the time the invention in this application was made*, so as to preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under

35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Again, the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/379,838, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Priority

6. Applicant's claim under 35 U.S.C. § 120 for benefit of the earlier filing date of the U.S. Patent Application No. 09/357,704, filed July 20, 1999, which claims benefit of U.S. Patent Application No. 08/838,682, filed April 9, 1997, which claims benefit of U.S. Provisional Application No. 60/022,125, filed July 18, 1996, and U.S. Provisional Application No. 60/016,976, filed May 6, 1996, is acknowledged.

However, claims 144, 156-168, 170-204, and 206-218 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 U.S.C. § 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of claims 144, 156-168, 170-204, and 206-218 is deemed the filing date of the instant application, namely August 13, 2001.

Grounds of Objection and/or Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments submitted as part of the papers filed October 11, 2007, have obviated or rendered moot the grounds of objection and/or rejection set forth in the previous Office action mailed April 11, 2007.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. The rejection of claims 144, 156-168, 170-204, and 206-218 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 16 of the amendment filed October 11, 2007, Applicant has traversed the propriety of maintaining this ground of objection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 144, 156-168, 170-204, and 206-218 are directed to a genus of antibodies or antigen-binding fragments thereof, which bind to PSMA and compete for binding to PSMA with a monoclonal antibody selected from the group consisting of a monoclonal antibody produced by

a hybridoma deposited under ATCC accession number HB-12101 (i.e., monoclonal antibody "E99"), a monoclonal antibody produced by a hybridoma deposited under ATCC accession number HB-12109 (i.e., monoclonal antibody "J415"), a monoclonal antibody produced by a hybridoma deposited under ATCC accession number HB-12127 (i.e., monoclonal antibody "J533"), and a monoclonal antibody produced by a hybridoma deposited under ATCC accession number HB-12126 (i.e., monoclonal antibody "J591").

As previously explained, the claims are indefinite because of the recitation in claim 144, for example, of "and competes for binding to PSMA with a monoclonal antibody" selected from the specified group of monoclonal antibodies.

Again, as also explained in the preceding Office action, at paragraph [0079], for example, of the published application[1], the specification discloses: "Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays". The specification describes the binding assay, which was used to determine, allegedly, whether monoclonal antibodies J591, J533, E99, and J415 detect the same or different epitopes; see, e.g., paragraphs [0104]-[0106] of the published application. As explained in paragraph [0105], the controls used as the basis for this determination consisted of using the same monoclonal antibody both cold and labeled to define "100% competition", or using monoclonal antibody to a totally different molecule (e.g., monoclonal antibody I-56, which detects inhibin) to define "0% competition". Thus, according to these disclosures, it is evident that one determines whether an antibody "competes" for binding to PSMA with one of the selected antibodies by measuring the percentage of binding of a detectably labeled antibody in the presence of an unlabeled (i.e., "cold") antibody.

Nevertheless, it is aptly noted that the term "competes" is not expressly defined in the specification, so it may not be immediately clear what functional attribute characterizes the claimed antibody or antigen binding fragment thereof; moreover, as discussed in greater detail below, the degree to which the claimed antibody "competes" for binding to PSMA with any one of the recited monoclonal antibodies, nor the methodology used to make the determination, and

[1] U.S. Patent Application Publication No. 2003/0003101 A1.

the conditions under which that determination are made, are not delineated by the claims and are not ascertainable from the disclosure.

The term "competition" is defined, for example, by Stedman's Online Medical Dictionary, 27th Edition as meaning: "The process by which the activity or presence of one substance interferes with, or suppresses, the activity of another substance with similar affinities" (Copyright © 2006 Lippincott Williams & Wilkins). Given this definition, the claims are directed to antibodies or antigen-binding fragments thereof that interfere with, or suppress binding of one of the selected monoclonal antibodies to PSMA, as perhaps determined using the exemplified binding assay.

This interpretation is not inconsistent with the specification, which at paragraph [0106], for example, discloses: "The results indicated that J591, J533, and E99 each **interfere, compete, or block** binding of one another but do not block binding of J415 and vice versa" (emboldened for emphasis).

Thus, while one may know how to determine whether an antibody "competes" with one of the selected monoclonal antibodies, it is apparent that the degree to which an antibody competes with another antibody is a relative or subjective expression, and the requisite degree to which the claimed antibody competes with any of the selected monoclonal antibodies cannot be ascertained from the disclosure.

Contrary to the assertion in the specification that such a binding assay determines whether two antibodies bind to the same antigenic determinant (i.e., epitope), competing antibodies do not necessarily bind the same epitopes. For example, "competing" antibodies may bind spatially overlapping but discrete epitopes. Simply because two antibodies cannot simultaneously occupy the same space, such an antibody, once bound to the antigen, sterically hinders or blocks binding of another such antibody. As another example, a "competing" antibody might not necessarily bind to the same epitope of an antigen as another antibody, if one of the antibodies induces conformational shifts in the three-dimensional structure of the antigen upon binding, which prevents binding of the other antibody to the antigen because the epitope to which it would otherwise bind is unrecognizable as a consequence of the structural change.

In addition, it is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

George et al. (*Circulation.* 1998; **97**: 900-906) (of record), for example, describes different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of competing with one another for binding to the antigen; see entire document (e.g., page 903, paragraph bridging columns 1 and 2). More particularly, George et al. describes three antibodies, which bind decidedly different, non-cross-reactive epitopes on β2GPI; yet, George et al. teaches each is able to "compete" *to some extent* with any of the others for binding to the antigen (page 903, paragraph bridging columns 1 and 2). For example, George et al. teaches monoclonal antibody ILA-4 competed with itself for binding to the antigen (% inhibition = 90 ± 11% at competitor antibody concentrations of 30 μg/ml), but George et al. discloses, despite its binding a non-overlapping epitope, monoclonal antibody ILA-1 also "competed", albeit perhaps unsubstantially with monoclonal antibody ILA-4 for binding to the antigen (% inhibition = 9 ± 4%).

Accordingly, George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification. Although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

Therefore, the claims are *not* unambiguously interpreted, as it cannot be determined whether the antibody to which the claims are directed is an antibody that merely inhibits, but does not abrogate the interaction between the selected antibody and PSMA. Moreover, if the claimed antibody merely inhibits binding of the selected antibody to PSMA, it cannot be

determined to what requisite extent the claimed antibody must "compete" for binding to PSMA with the selected antibody.

Beginning at page 16 of the amendment filed October 11, 2007, Applicant has remarked that the term "competes" is not ambiguous; in reply, it is not the term that is ambiguous, but rather the claims that recite that term, since, for example, it cannot be determined whether the claimed antibody merely inhibits binding of the selected monoclonal antibody to PSMA, or rather necessarily abrogates the interaction between PSMA and the monoclonal antibody, because the claims do not make evident that extent to which the interaction is inhibited.

Applicant has further remarked that the skilled artisan would be able to determine if an antibody competes with any one of the monoclonal antibodies produced by the deposited hybridomas; although it is true, since one skilled in the art could in fact *qualitatively* determine if any two antibodies compete for binding to an antigen; but, as explained, it cannot be ascertained to what extent the antibody to which the claims is directed must "compete" for binding to PSMA with the monoclonal antibody. Because the extent to which an antibody might compete with the selected monoclonal antibody may vary substantially, depending, for example, upon the conditions under which that extent is measured, the metes and bounds of the subject matter that might be encompassed by the claims is expected to vary extensively; but rather than just merely broad, it is submitted that the claims fail to delineate those metes and bounds that are regarded as the invention with the clarity and particularity necessary to permit the skilled artisan to know or determine infringing subject matter.

For example, it might be argued that an antibody that specifically binds to PSMA, though not necessarily at a site recognized by any one of monoclonal antibodies J591, J533, E99, and J415, is capable of competing for binding to PSMA, at least to some measurable extent, with one of these monoclonal antibodies.

This position is not unreasonable in view of the disclosure by George et al. (of record), which as explained describes antibodies that bind decidedly different, non-cross-reactive epitopes on an antigen, but which are nonetheless capable of "competing" *to some extent* with each of the others for binding to the antigen.

So, with this point in mind, might the claims be properly construed to read on any antibody that binds to PSMA, including any of the antibodies disclosed by the prior art (e.g., monoclonal antibody 7E11-C5.3, as described, for example, by Troyer et al. (of record; cited by Applicant))?

Presumably Applicant does not intend to claim an antibody of the prior art as their invention; but if not such an antibody, then which antibody are considered the invention? Which antibodies that bind to PSMA are not encompassed by the claims? How might one distinguish an antibody that is regarded by Applicant as part of the invention from any other antibody that also binds to PSMA?

As submitted, the claims would not permit the skilled artisan to know or determine whether any given antibody that binds PSMA is, or is not encompassed by Applicant's claims, since it cannot be known to what extent the antibody does or does not compete for binding to PSMA with any one of monoclonal antibodies J591, J533, E99, and J415.

Applicant has further argued that the Office's characterization of the disclosure of George et al., as illustrating the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification, is inaccurate. Applicant has contended to the contrary that the artisan is fully capable of determining whether or not an antibody "competes" for binding to an antigen with another antibody.

In reply, it is not contested that the artisan is capable of making a determination based upon the results of a competitive binding assay, such as the assay exemplified in the specification, that one antibody "competes" for binding with another; accordingly, the relevant point made in citing George et al. to support of the propriety of this ground of rejection is that the degree to which one antibody competes for binding to an antigen with another is expected to vary substantially, depending upon the binding specificities and affinities of the antibodies used in the assay, such that one might arbitrarily label the antibodies as either binding to "competing" or "non-competing" binding sites".

Notably Applicant has contended that the antibodies disclosed by George et al. do "compete", despite the opposite conclusion by George et al. that the antibodies do not. These

remarks support the Office's position that the artisan cannot know the requisite degree to which the claimed antibody must compete for binding to PSMA with the selected monoclonal antibody; and as such, the claims cannot be regarded as delineating the subject matter that is regarded as the invention with the necessary clarity and particularity to permit the skilled artisan to know or determine infringing subject matter.

Beginning at page 17 of the amendment, Applicant has further remarked that, just as George et al. had presumably done, the practitioner of the claimed invention may carry out scientific experiments to determine a "reasonable threshold for competition", which identifies an antibody that is to be used in its practice. Moreover, Applicant has remarked that skilled artisans routinely carry out planned and controlled experiments to determine whether antibodies compete with one another, and they would not arbitrarily add a concentration of an antibody so high as to give false positive results without testing other concentrations.

It is submitted that these remarks also support the Office's position that the claims are indefinite. The subject matter that is the claimed invention must be defined by the claims with clarity and particularity; the subject matter encompassed by the claims must not vary, but must instead by known or readily determinable. If, as Applicant's remarks might suggest, the practitioner of the claimed invention may carry out scientific experiments to determine a "reasonable threshold for competition", which presumably identifies an antibody that is to be used in its practice, the antibody to which the claims are directed is not limited to any clearly or particularly defined antibody; rather, the antibody might be any antibody that is somehow determined, perhaps arbitrarily so, to compete for binding to PSMA with the selected antibody, and thus the subject matter encompassed by the claims might vary significantly, depending upon just how high or low that "reasonable threshold for competition" is set.

It follows that if one cannot determine the requisite degree to which the claimed antibody competes for binding to PSMA with the selected monoclonal antibody, because there is no known or disclosed standard for ascertaining this requisite degree, which may perhaps be similar, if not equivalent to Applicant's "reasonable threshold for competition", then how might the subject matter encompassed by the claim be known or determined? How might one reasonably conclude that the claims have delineated that subject matter, which is regarded as the invention,

with the necessary clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph?

Finally, it is noted that Applicant has argued that a determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing.

The Examiner disagrees; while the methodology used to determine whether or not an antibody competes for binding to an antigen with another antibody may have been practiced routinely, the outcome, i.e., the conclusion reached by such experiments is not founded upon any well-established procedure or guideline, which unambiguously and consistently provides one with accurate, objective, and certain knowledge that the antibodies either compete for binding to the antigen or do not. Again, Applicant has contended that the antibodies disclosed by George et al. do compete (Applicant's emphasis), despite the opposite conclusion by George et al. that the antibodies do not. So, while the methodological approach used by Applicant, as well as by George et al. to determine if an antibody competes for binding to an antigen with another antibody may have been routine at the time this application was filed, it is apparent that there was no consensus as to the requisite degree one antibody necessarily inhibits binding of the other before it is labeled a "competing" or a "non-competing" antibody (i.e., the value of the threshold level of inhibition that is observed in such assays, which defines the antibody as either a "competing" or a "non-competing" antibody, has not been established).

Therefore, without intending to acquiesce to Applicant's argument that a determination of whether or not an antibody competes for binding with another antibody was a well-established procedure at the time of filing, it is noted that Applicant has remarked that George et al. describes scientific experiments in which the "reasonable threshold for competition", i.e., 5-9% inhibition, indicated no competition. Might these remarks suggest that if any given antibody inhibits the binding of the selected antibody to a more significant extent (e.g., wherein at least 10% inhibition has been observed in a competition binding assay similar to that which has been disclosed in this application), the antibody is an antibody that is encompassed by the claims? Again, despite the routine nature of the methodology that might be used to determine if an antibody competes for binding to PSMA with the selected antibody, it would seem that

Applicant's "reasonable threshold for competition" may vary substantially. Though a poorly competing antibody might not be reasonably expected to bind to the same epitope of PSMA as the selected monoclonal antibody, the claims are not so limited; and because it cannot be ascertained to what requisite extent the claimed antibody is capable of competing for binding to PSMA with the selected antibody, the claimed antibody might be any antibody that at least partially inhibits binding of the selected monoclonal antibody to PSMA. In that case, then, the claims should be read as encompassing antibodies of the prior art. Therefore, absent a disclosure describing the value of the threshold of inhibition that defines the extent to which the claimed antibody must compete, there are no means for establishing the metes and bounds of the subject matter that is encompassed by the claims and regarded by Applicant as the invention.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. The rejection of claims 178 179, and 214 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Beginning at page 19 of the amendment filed October 11, 2007, Applicant has traversed the propriety of maintaining this ground of rejection, arguing that it is not important whether the actual language of the claims finds support in the specification.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As Applicant has correctly noted, the written description requirement is met if the specification show that an applicant was in possession of the claimed invention at the time the application was filed. Claims 178, 179, and 214 are directed to a genus of "cells" that produces

an antibody that competes for binding to PSMA with a selected monoclonal antibody. Claim 179 is more particularly directed to members of this genus of such cells, which are derived from a lymphocytic cell line. However, none of originally filed claims nor any of the particular disclosures describes a genus of cells, including such cells derived from a lymphocytic cell line, which produce an antibody that competes for binding to PSMA with a selected monoclonal antibody.

As previously explained, claims 178 and 179 were added by the amendment filed March 22, 2002[2]. At page 8 of that amendment Applicant has asserted that support for these claims is found in the specification, as filed, in the originally filed claims, as well as in the disclosure, e.g., at page 16, line 16, through page 17, line 4; page 25, lines 16-35; page 35, Table 3); page 19, lines 20-36 and Table 1; page 11, lines 21-33; page 37, line 24, through page 39, line 14; page 18, line 33, through page 19, line 7; page 40, line 14, through page 45, line 14; page 20, line 1, through page 29, line 10; page 21, lines 19-30; and page 6, lines 5-22.

Contrary to Applicant's assertions, none of these disclosures provide an adequate description of the claimed genus of "cells".

Originally filed claims 64-67 (now canceled) were drawn to a genus of **hybridomas** that produce an antibody that binds the extracellular domain of PSMA, including the deposited hybridomas that produced monoclonal antibodies E99, J415, J533, and J591. A "hybridoma" is "a hybrid cell produced by the fusion of an antibody-producing lymphocyte with a tumor cell and used to culture continuously a specific monoclonal antibody" (Merriam-Webster Online Dictionary; Copyright © 2005 by Merriam-Webster, Inc.).

However, a description of a "hybridoma" should not be deemed to suffice as a description of any cell, only a hybrid cell produced by fusing an antibody-producing lymphocyte and a tumor cell; thus it is submitted that none of the originally filed claims is reasonably considered to describe with the requisite degree of clarity and particularity the broader genus of "cells" to which claim 178 is directed, and none describe the subgenus of cells, which are derived from a lymphocytic cell line, to which claim 179 is directed.

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[2] Claim 214 has just been added by the amendment filed October 11, 2007.

Similarly, the originally filed disclosure describes these same **hybridomas**, but does not describe with any degree of particularity a genus of "cells" that produce an antibody that competes for binding to PSMA with any of the monoclonal antibodies produced by those hybridomas. For example, at paragraph [0033] of the published application, the specification describes **hybridoma** cell lines, which produce monoclonal antibodies that recognize an extracellular domain of PSMA, bind PSMA and/or are internalized with PSMA. Then, at paragraph [0054] of the published application, the specification discloses production of such monoclonal antibodies may be effected by techniques, which are well-known in the art and basically involve: (a) obtaining immune cells (i.e., lymphocytes) from the spleen of a mammal (e.g., mouse) that has been previously immunized with the antigen of interest, and (b) fusing the antibody-secreting lymphocytes with mouse myeloma cells or other transformed cells, which are capable of replicating indefinitely in cell culture, so as to produce **immortal, immunoglobulin-secreting cell lines, or hybridomas**, which are then cultured and screened for the production of the desired monoclonal antibodies. None of these disclosures, however, describes with any degree of particularity the genus of "cells" to which the claims are directed, as none describes the type and nature of the cells, apart from **hybridomas**, producing such antibodies, and especially not such cells that are derived from a lymphocytic cell line, per se.

Consequently, the addition of 178 and 179 appears to have introduced new matter, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Beginning in the last paragraph at page 20 of Applicant's response filed October 11, 2007, it has been argued that the skilled artisan would find implicit in the disclosure of the routine methodology by which hybridomas are generated a description of the immune cells (i.e., lymphocytes) from the spleen of a mammal (e.g., mouse) that has been previously immunized with the antigen of interest, which necessarily produce the antibody to which the claims are directed.

In response, the claims are directed to a member of a genus of cells that produce an antibody having the requisite binding properties; according to the claims the cell is *isolated.* The immune cells that produce the antibody are not isolated from immune cells not producing the

antibody; rather, as disclosed at paragraph [0033] of the published application, for example, immune cells, as a whole, are acquired from the spleen of the previously immunized animal and then fused, as a whole, with mouse myeloma cells or other transformed cells, which are capable of replicating indefinitely in cell culture, so as to produce a plurality of hybridomas, which are then cultured and screened for the production of the desired monoclonal antibodies. Only after screening members of the plurality of hybridomas produced is a hybridoma producing an antibody having the requisite binding properties isolated from hybridomas not producing an antibody having the requisite binding properties; and accordingly, it is submitted contrary to Applicant's argument that the skilled artisan would **not** find implicit in the disclosure of the routine methodology by which hybridomas are generated a description of the particular isolated immune cells (i.e., lymphocytes) acquired from the spleen of a mammal (e.g., mouse) that has been previously immunized with the antigen of interest, which produce *the* antibody to which the claims are directed.

Arguendo, if the disclosure of the methodology by which the plurality of immune cells producing antibodies acquired from the spleen of the immunized animal were believed sufficient to describe the particular *immune* cell that produces the antibody having the requisite binding activity, it should not be considered adequate to describe any cell (e.g., a recombinant cell produced by transfecting the cell with a nucleic acid encoding the antibody) that produces the antibody – but only the immune cell that produces the antibody (i.e., a B-lymphocyte).

Accordingly, although Applicant's arguments have been carefully considered, this ground of rejection has been maintained[3].

12. The rejection of claims 144, 156-168, 170-204, and 206-218 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The

[3] Beginning at page 19 of the amendment filed October 11, 2007, it is noted that Applicant has remarked that claims 181-183, 204, 206, and 207 have been amended so as to be directed to a kit for detecting prostate epithelial cells; contrary to this remark, however, the claims, as presently amended, are more narrowly directed to a kit for detecting prostate cancer. As previously explained, originally filed claims 59-63 (now canceled) were directed to a kit for detecting prostate cancer; and furthermore the specification describes at paragraph [0052] of the published application, for example, methods of detecting normal, benign hyperplastic, and cancerous prostate epithelial cells, which certainly provides implicit support for claims directed to kits for performing such methods. Consequently, the amendment to claims 181-183 and the addition of 204, 206, and 207 appears to have remedied the issue of new matter raised in the preceding Office action.

claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection, as opposed to a "new matter" rejection. As explained in the preceding Office action, it is believed that the following are grounds of rejection, *which were not before addressed or considered by Applicant, the Office, or the Board of Patent Appeals and Interferences.*

Beginning at page 21 of the amendment filed October 11, 2007, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Again, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter, the "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

As presently amended, the claims are directed to a genus of antibodies that bind to PSMA and compete for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591 monoclonal antibody produced by hybridomas deposited under ATCC accession numbers HB-12101, HB-12109, HB12127, and HB-12126, respectively.

As explained in the above rejection of claims under 35 U.S.C. § 112, second paragraph, the claims are not necessarily limited to antibodies that completely abrogate the interaction between any member of the recited pluralities of antibodies and PSMA, nor are the claims necessarily limited to antibodies that bind to the same antigenic determinant (i.e., epitope) of PSMA as any of the recited antibodies. To the contrary, when given the broadest, *reasonable* interpretation that is both consistent with the specification and that which would be understood by the skilled artisan, the claims are directed to any antibody or antigen-binding fragment thereof

that inhibits or suppresses, at least to some measurable extent, binding of any member of the recited pluralities of antibodies to PSMA.

George et al. (cited *supra*) teaches that even antibodies that decidedly do not bind overlapping epitopes are able to compete to some measurable extent with other antibodies that bind the same antigen; and it is again submitted, as above, that any antibody, regardless of its antigenic binding specificity, is capable at high enough concentrations to at least partially inhibit binding of another antibody to an antigen recognized by that other antibody.

Accordingly, because the requisite degree to which the claimed antibody or antigen-binding fragment "competes" with any member of the recited pluralities of monoclonal antibodies for binding to PSMA is not specified by the claims, and is not ascertainable from the disclosure, the claims should be broadly interpreted to read on virtually any other antibody that binds PSMA, though not necessarily an antibody that binds the same, or even an overlapping epitope of PSMA, and not necessarily an antibody that competes for binding to PSMA to any particular extent, provided it competes to a measurable extent under some unspecified conditions.

As evidenced by George et al. (cited *supra*), for example, an antibody need not bind to the same, or even an overlapping epitope to exhibit some ability to "compete" for binding to an antigen with another antibody; if follows, especially at high enough concentrations, that any antibody that binds PSMA, regardless of its fine binding specificity, might under certain conditions compete for binding to an antigen with another antibody that binds that antigen, including, for example, any of monoclonal antibodies J591, J533, E99, and J415.

In contrast to the breadth of the claims, the specification describes with particularity only five different antibodies that bind PSMA: 7E11/CYT356, J591, J533, E99, and J415. The first of these antibodies is described by the prior art as binding the intracellular domain of PSMA, whereas the other antibodies (J591, J533, E99, and J415) are described in the specification as binding to the extracellular domain of the antigen. At paragraph [0106], for example, the specification discloses J591, J533, and E99 each interfered with binding of one another but did not block binding of J415, and vice versa; and 7E11/CYT356 did not block binding of any of J591, J533, E99, and J415.

Accordingly, the specification describes three antibodies that "compete" for binding to PSMA with one another, namely J591, J533, and E99; and it also describes two other antibodies (i.e., 7E11 and J415), which do not compete with any of the other antibodies that have been described.

Because each of monoclonal antibodies J591, J533, and E99 interferes with the others, the specification describes each as binding to the *same* epitope of PSMA; see, e.g., Example 10 at paragraphs [0104]-[0108] of the published application. Because none of monoclonal antibodies J591, J533, and E99 interferes with the binding of monoclonal antibodies 7E11/CYT356 or J415, the specification teaches these latter antibodies bind to *different* epitopes of PSMA.

It is submitted that there is inadequate description of the claimed genus of antibodies or antigen-binding fragments that compete for binding to PSMA with monoclonal antibody J415 to reasonably convey Applicant's possession of the claimed invention at the time the application was filed. Again, none of monoclonal antibodies J591, J533, E99, and 7E11/CYT356 are described as having the ability to "compete" for binding to PSMA with monoclonal antibody J415; moreover, no where in the specification is there literal support, much less any particular description of antibodies that compete for binding to PSMA with monoclonal antibody J415.

To the contrary, there may be in fact be implicit, if not explicit written support in the specification, as filed, for claims directed to a genus of antibodies or antigen-binding fragments thereof that bind PSMA, which compete for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibodies J591, J533, and E99.

Nevertheless, although the present claims are not original claims, the "Guidelines" (cited *supra*) state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and

> there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

The Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, although the specification, as filed, may provide written support for the language of the claims, the disclosure must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

It is submitted that the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed subject matter at the time the application was filed because it fails to adequately describe the genus of antibodies or antigen-binding fragments that bind specifically to PSMA and thereby "compete" for binding to the antigen with any one of the recited monoclonal antibodies.

It is further submitted that the claims, if indeed properly supported by the specification, as filed, should be *solely* directed to antibodies or antigen-binding fragments that bind to the *same* epitope as any of member of the recited pluralities of monoclonal antibodies (e.g., an E99 monoclonal antibody) and thereby compete for binding to PSMA with the particular member, or alternatively to antibodies or antigen-binding fragments that bind to a *different* epitope of PSMA and do not compete for binding to PSMA with the particular member. More pointedly, antibodies that "compete" for binding to PSMA with any of the recited monoclonal antibodies, which bind *overlapping* epitopes of PSMA, have not been described.

The specification insufficiently describes members of the genus of antibodies or antigen-binding fragments that bind antigenic determinants or epitopes of PSMA that are not recognized by any of monoclonal antibodies each of monoclonal antibodies J591, J533, and E99, which are able to compete with any of the latter for binding to PSMA. Again, although such antibodies or antigen-binding fragments thereof recognize epitopes that are distinct from those recognized by any of monoclonal antibodies each of monoclonal antibodies J591, J533, and E99, as evidenced by George et al. (cited supra), for example, antibodies need not bind the same epitope, or even an overlapping epitope of an antigen to "compete" with another antibody for binding to the antigen. The specification does not describe particularly identifying structural and/or functional features, which would permit the skilled artisan to immediately envision, recognize, or distinguish at least a substantial number of the members of the claimed genus of antibodies or antigen binding fragments thereof, which bind to epitopes that differ from those recognized by monoclonal antibodies J591, J533, E99, or J415, or any other antibody to which the claims are directed. For example, the specification fails to describe the claimed genus in such a clear and particular manner to permit the skilled artisan to readily distinguish an antibody that binds to PSMA, *and* competes for binding to PSMA with monoclonal antibodies J591 or J415, from another antibody that also binds the antigen *but* does not compete with such a monoclonal antibody.

Furthermore, the specification insufficiently describes members of the genus of antibodies or antigen-binding fragments that bind the same antigenic determinants or epitopes of PSMA recognized by monoclonal antibodies J591, J533, and E99 and are accordingly able to compete with any of the latter for binding to PSMA. The specification fails to describe reliably predictable means for determining whether an antibody that binds PSMA binds to the same epitope of the antigen as any of monoclonal antibodies J591, J533, E99, or J415, or any other monoclonal antibody to which the claims are directed. As explained in greater detail below, the competition binding assay that has been exemplified cannot be used to establish with certainty whether two "competing" antibodies bind to the same epitope of an antigen; and furthermore, the conditions under which the assay is to be used to identify the claimed antibodies, which do or do not bind the same epitope, but which nevertheless "compete" with one of the recited monoclonal antibodies have not been described. For these reasons, the specification would not reasonably

convey to one skilled in the art that Applicant had possession of the claimed invention at the time the application was filed.

Due to the unpredictable nature of the art, where the claimed antibodies are perhaps functionally related by their common abilities to "compete" with one of the recited monoclonal antibodies, but unrelated structurally, absent sufficient description of the claimed invention, those that bind particular epitopes of PSMA cannot be envisioned, recognized or distinguished from other antibodies that also bind PSMA, albeit by the recognition of different epitopes. The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Where the claimed antibodies are functionally related as binding a common epitope of PSMA, whether the antibodies are or are not structurally related, the specification fails to describe the epitope to which the claimed antibodies bind. "[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of antibodies that bind any one particular epitope of PSMA, such as the epitope to which monoclonal antibody J591 binds, because no one particular epitope of PSMA to which such an antibody binds has been described with clarity or particularity to permit the skilled artisan to recognize that Applicant's had knowledge of that epitope or possession of the claimed plurality of antibodies that recognize that epitope. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

In this instance, the claims are directed to a genus of antibodies that includes, but are not necessarily limited to antibodies that bind to PSMA, which, at least in structural terms, is generally considered a fully characterized antigen; however, the difference here is, although the antibodies bind PSMA, they only bind very particular epitopes of PSMA that recognized by other monoclonal antibodies, such as monoclonal antibody J591, and are thereby able to "compete" with the latter for binding to PSMA. The specification describes these epitopes as residing in the extracellular domain of PSMA; see, e.g., paragraph [0029] of the published application. None of the epitopes to which any of the disclosed monoclonal antibodies binds have been described with the requisite degree of particularity however to permit the skilled artisan to recognize those epitopes.

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, were the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. However, the claims are not directed to an antibody that binds a well-characterized molecular target, but rather to an antibody that binds to *very discrete parts (i.e., epitopes) of PSMA*, which has not been characterized and remain cryptic in nature.

The term "epitope", as it is used in the art of immunology, is more generally used in a broader context to mean an "antigenic determinant", or site on the surface of an antigen molecule to which a single immunoglobulin molecule (e.g., antibody) binds; generally an antigen has several or many different antigenic determinants and reacts with antibodies of many different specificities. Stedman's Online Medical Dictionary, 27th Edition, which is available on the Internet at http://www.stedmans.com/, for example, defines the term "epitope' as "[t]he simplest form of an antigenic determinant, on a complex antigenic molecule, which can combine with antibody or T cell receptor".

Notably, Greenspan et al. (*Nature Biotechnology*. 1999; **7**: 936-937), for example, teaches that defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include any and all residues that make contact with a ligand, here an antibody; even contacts by residues that are energetically neutral, or even destablilizing to

binding are constitutive. Greenspan et al. teaches an epitope will not include any residue not contacted by the ligand (i.e., an antibody), even though substitution of such a residue by another might profoundly affect binding. Accordingly, it follows the epitope to which any given ligand binds can only be identified empirically.

Thus, even using a competition binding assay, such as that described in Example 10 of the specification, the skilled artisan cannot recognize or distinguish an antibody that binds the same epitope as another antibody because antibodies that compete with one another for binding to the same antigen do not necessarily bind the same epitope; rather, an antibody may bind a spatially overlapping epitope and thereby sterically hinder binding of the other ligand to its epitope, or as evidenced by George et al. (cited *supra*), an antibody may bind an epitope that is distant from, and spatially non-overlapping with the epitope of an antigen recognized by the other antibody, and still interfere with binding of the latter to the antigen.

Where the claimed antibodies bind an epitope of PSMA recognized by any of the recited monoclonal antibodies, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to bind a particular epitope of PSMA, or the ability to "compete" for binding to PSMA with any of the recited monoclonal antibodies, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can

provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). Without the antibodies to which the claims are directed, it is impossible to make or use the claimed invention.

In addition, although the skilled artisan could initially screen candidate antibodies to identify those that are possibly encompassed by the claims by performing, for example, a competitive binding assay, and then empirically determine whether the selected antibodies bind to the same epitope recognized by one of the recited monoclonal antibodies, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating (or identifying) it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

"Guidelines" (cited *supra*) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of antibodies, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant

has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

At page 22 of the amendment filed October 11, 2007, Applicant has remarked that it is their position that Board of Patent Appeals and Interferences has already decided in favor of Applicant in this matter.

In reply, as explained previously, this is a "written description" rejection, as opposed to a "new matter" rejection. It is firmly believed that these grounds of rejection were *not before* addressed or considered by Applicant, the Office, or the Board of Patent Appeals and Interferences.

In addition, as has been explained, while it might be presumed that Applicant does not intend to claim an antibody of the prior art as their invention, it is not evident how one might immediately recognize or distinguish an antibody that is regarded by Applicant as part of the invention from any other antibody that also binds to PSMA; so if the invention is not an antibody of the prior art, which binds PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, then what is considered the invention?

The claims would not permit the skilled artisan to know or determine whether any given antibody that binds PSMA is, or is not encompassed by Applicant's claims, since it cannot be known to what extent the antibody does or does not compete for binding to PSMA with any one of monoclonal antibodies J591, J533, E99, and J415. If so, then, the disclosure cannot be considered an adequate description of the subject matter that is now claimed. Accordingly, the written description requirement set forth under 35 U.S.C. § 112, first paragraph, cannot have been met by Applicant's disclosure.

Applicant has submitted that the disclosure of a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively,

suffices to describe any antibody that binds PSMA and competes for binding to PSMA with one of these monoclonal antibodies.

Which of these monoclonal antibodies competes with monoclonal antibody J415, as produced by the hybridoma deposited under accession number HB-12019?

The specification describes three antibodies that "compete" for binding to PSMA with one another, namely J591, J533, and E99; and it also describes two other antibodies (i.e., 7E11 and J415), but discloses that neither one competes with any of the other antibodies that are described; see, e.g., paragraph [0106] of the published application.

So, while the specification may describe three antibodies capable of competing with one another for binding to PSMA, it describes two others that do not.

Where in the specification is there a suggestion that Applicant contemplated, as of the filing date of the instant application, any of a plurality of antibodies that binds PSMA and competes for binding with any one of monoclonal antibodies J591, J533, E99, and J415?

Moreover, why would Applicant's disclosure at paragraph [0106] of the published application reasonably convey to the skilled artisan that Applicant had possession of any of a plurality of antibodies that binds to PSMA and competes for binding with any one of monoclonal antibodies J591, J533, E99, and J415?

Paragraph [0106] of the published application reads as follows:

> The results indicated that J591, J533, and E99 each interfere, compete, or block binding of one another but do not block binding of J415 and vice versa. 7E11/CYT356, known to bind PSMA at a different (intracellular) site, did not block any of J591, J533, E99, or J415.

Paragraph [0106] fails to describe an antibody that binds to PSMA, which competes for binding to PSMA with monoclonal antibody J415; and although it describes three antibodies that are capable of interfering with one another, how might such a description suffice to permit the skilled artisan to immediately envision, recognize, or distinguish at least a substantial number of other anti-PSMA antibodies, which are similarly capable of competing for binding to PSMA with any of the particularly described monoclonal antibodies?

As explained, if any given anti-PSMA antibody happens to bind to the same, or even an overlapping epitope as another, it would be expected to compete for binding to PSMA with the

other; but then again, under certain conditions, any anti-PSMA antibody might be deemed capable of "competing" for binding to PSMA with another.

Again, George et al. (cited *supra*) teaches that even antibodies that decidedly do not bind overlapping epitopes are able to compete to some measurable extent with other antibodies that bind the same antigen.

Accordingly, because the requisite degree to which the claimed antibody or antigen-binding fragment "competes" with any member of the recited pluralities of monoclonal antibodies for binding to PSMA is not specified by the claims, and is not ascertainable from the disclosure, the claims should be broadly interpreted to read on virtually any other antibody that binds PSMA, though not necessarily an antibody that binds the same, or even an overlapping epitope of PSMA, and not necessarily an antibody that competes for binding to PSMA to any particular extent, provided it competes to a measurable extent under some unspecified conditions. So what particularly identifying properties distinguishes the claimed antibody from others, and particularly from the other anti-PSMA antibodies, which are taught by the prior art? What structural and/or functional properties are shared by monoclonal antibodies J591, J533, E99, and J415, and are also shared by other members of the claimed genus of antibodies, might permit the skilled artisan to recognize or distinguish those other members?

It would appear that each of the monoclonal antibodies has a distinct structure, since each is produced by a different hybridoma, so it seems unlikely that the claimed monoclonal antibodies might be recognized or distinguished by a comparison of their structures and the structures of other anti-PSMA antibodies, which are not regarded as part of the invention.

Furthermore, although three of the antibodies compete for binding to PSMA with each other, one does not, so it follows that even the functional capability of competing for binding to PSMA with one of the four monoclonal antibodies would not necessarily permit the artisan to immediately recognize or distinguish those antibodies that encompassed by the claims from those that are not.

Still, what if an antibody that binds to PSMA is found capable of competing with one of the monoclonal antibodies, is it to be regarded as part of the invention, and might have the

disclosure, as filed, conveyed to the skilled artisan that Applicant had in their possession that antibody at the time the application was filed?

Of course, if it cannot be ascertained to what requisite extent the antibody must compete for binding to PSMA with the selected antibody it cannot be determined whether it is in fact part of the invention. Again, the prior art's anti-PSMA antibody that binds to PSMA and is capable of competing to some measurable extent for binding to PSMA with one of monoclonal antibodies J591, J533, E99, and J415 is presumably not subject matter regarded as the invention, so there must be a limitation, though not recited in the claims or ascertainable from the disclosure, as to just how effective the claimed antibody necessarily competes.

Beginning at page 23 of the amendment filed October 11, 2007, Applicant has further traversed the propriety of maintaining this ground of rejection, contending that the antibodies disclosed by George et al. do not "compete", despite all evidence to the contrary.

Again, George et al. discloses, despite its binding a non-overlapping epitope, monoclonal antibody ILA-1 also "competed", albeit perhaps unsubstantially with monoclonal antibody ILA-4 for binding to the antigen (% inhibition = 9 ± 4%).

The disclosure by George et al. supports the Office's position that the artisan cannot know the requisite degree to which the claimed antibody must compete for binding to PSMA with the selected monoclonal antibody to be regarded or recognized as the invention; and as such, the claims cannot be regarded as delineating the subject matter that is regarded as the invention with the necessary clarity and particularity to permit the skilled artisan to recognize in the disclosure an adequate description of that subject matter. Therefore, the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

At page 24 of the amendment Applicant has asserted that the disclosure of monoclonal antibody J415, itself, is a description of an antibody that competes for binding to PSMA with the antibody.

The Examiner rejects this argument as wholly lacking scientific merit. The claims are not directed to monoclonal antibody J415, but are instead directed to an antibody that binds to PSMA and competes for binding to PSMA with monoclonal antibody J415. It is submitted that

the skilled artisan would not reasonably conclude that an antibody capable of competing with another antibody is adequately described by the mere description of the other antibody, in part, because it would be generally understood that the claimed antibody and monoclonal antibody J415 are at least patentably or unobviously different[4].

Nonetheless, it is submitted that Applicant's remark supports the Office's position that the claims fail to delineate the subject matter that is regarded as the invention with the necessary clarity and particularity to permit the skilled artisan to recognize in the disclosure an adequate description of that subject matter. Applicant has argued that at least one member of the claimed genus of antibodies that competes with monoclonal antibody J415 is disclosed, namely the labeled monoclonal antibody. The competition assay is typically performed using a very small, nearly negligible amount of a labeled antibody. Quantitatively, such a trace amount of labeled antibody interferes little with binding of the substantially larger amount of unlabeled antibody that is also present in the assay. As such, since it is Applicant's position that the inclusion of the labeled antibody in the competition assay would suffice to describe the claimed antibody that competes with (unlabeled) monoclonal antibody J415, it would appear that nearly negligible levels of interference are all that might be required of the claimed antibody. Again, this would suggest that the claims are broadly, but reasonably interpreted to encompass any antibody that binds to PSMA, which under certain conditions is capable of competing at least to some measurable extent for binding to PSMA with monoclonal antibody J415 (e.g., any antibody that binds to PSMA, which has been described by the prior art); however, since it is again presumed that Applicant does not regard such antibodies of the prior art as their invention, it becomes apparent that the disclosure would not permit the skilled artisan to immediately envision, recognize, or distinguish those antibodies that are regarded as the invention because it fails to describe the extent to which those antibodies must compete.

Finally, at page 25 of the amendment, Applicant has remarked that since term "epitope" is absent from the claims, the Office has unnecessarily read limitations into the claims. In reply, the claims are interpreted in light of the specification.

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[4] The addition of a label to an antibody is not expected to substantially alter its function.

Contrary to the assertion in the specification, a competition binding assay does not determine whether two antibodies bind to the same antigenic determinant (i.e., epitope), since competing antibodies do not necessarily bind the same epitopes; and besides, since typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody, at *high enough* concentrations, any antibody that binds to PSMA might be deemed capable of "competing" for binding to PSMA with any other antibody, including any one of monoclonal antibodies J591, J533, E99, and J415, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

None of the epitopes to which any of monoclonal antibodies J591, J533, E99, and J415 have been described with particularity; and it cannot be ascertained whether any of these monoclonal antibodies bind to the same epitope, simply on the basis that three of the four compete with one another for binding to PSMA.

Accordingly, although Applicant's arguments have been carefully considered, this ground of rejection has been maintained.

13. The rejection of claims 144, 156-168, 170-204, and 206-218 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a monoclonal antibody selected from the group consisting of J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, an antigen-binding fragment thereof, a composition comprising said antibody or antigen-binding fragment, a kit for detecting prostate cancer comprising said antibody or antigen-binding fragment, and a hybridoma selected from the group consisting of the hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, **and while being enabling for making and using** an antibody or antigen binding fragment thereof described by the prior art, which is encompassed by the claims, a composition or kit comprising such an antibody or antigen binding fragment described by the prior art, as well as a hybridoma or other cell line producing such an antibody, **does not reasonably provide enablement for making and/or using** any antibody or antigen-binding fragment that binds to PSMA and competes for binding to PSMA with a monoclonal

antibody selected from the group consisting of E99, J415, J533 and J591 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, an composition thereof, a kit for detecting any type of cancer comprising such an antibody or antigen-binding fragment thereof, or a cell that produces such an antibody, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Beginning at page 23 of the amendment filed October 11, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Again, M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In this instance, as previously explained, the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and./or unreasonable experimentation.

As noted in the rejections above (e.g., the rejection of claims under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement), the claims are directed to a genus of anti-PSMA antibodies or antigen-binding fragments thereof, which are capable of competing for binding to PSMA with any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, but which do not necessarily bind to the same epitope as the selected monoclonal antibody.

Even so, the claimed antibodies or antigen binding fragments thereof, which compete for binding to PSMA with any of a plurality of recited monoclonal antibodies, include antibodies or antigen-binding fragments that *do* bind to the same epitope as a member of any of the recited monoclonal antibodies. Support for this interpretation is found throughout the specification, as filed; see, e.g., paragraph [0104] of the published application.

As explained above, the specification describes monoclonal antibodies J591, J533, and E99 as each capable of interfering with binding of the others to PSMA but incapable of competing for binding to PSMA with monoclonal antibodies J415 and 7E11/CYT356, and vice versa. Because each of monoclonal antibodies J591, J533, and E99 interferes with the others, the specification teaches each binds to the same epitope of PSMA; and because none of monoclonal antibodies J591, J533, and E99 interfere with the binding of monoclonal antibodies J415 and 7E11/CYT356, and vice versa, the specification teaches the latter antibodies bind different epitopes.

However, as also explained above in the rejections of claims under 35 U.S.C. § 112, first and second paragraphs, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what conditions. As evidenced by George et al. (cited supra), for example, at a high enough concentration, or under certain conditions, *any* antibody is

expected to "compete" for binding to the antigen with the other antibody; though perhaps another antibody that binds the same antigen, or more particularly the same epitope of an antigen or an overlapping epitope recognized by a given antibody would be expected to more effectively compete than an antibody that binds to some other antigen or a distinct portion of the same antigen.

So, therefore, an antibody that competes for binding does not necessarily bind to the same epitope as another antibody. Rather, an antibody may bind a spatially overlapping, but distinct epitope of PSMA, and still compete for binding to PSMA with one of the recited monoclonal antibodies.

This is because antibodies that bind overlapping epitopes of the same antigen act to sterically inhibit binding of others, even though each recognizes a discrete epitope of the antigen; so, a competition-binding assay can thus not serve to identify antibodies that bind the same epitope.

Accordingly, to whatever extent the claims are drawn to an antibody or antigen binding fragment that binds to the same epitope as any one of the recited monoclonal antibodies, so as to be capable of competing with the latter for binding to PSMA, it is submitted that it would not be a merely routine matter to make the claimed antibody that is capable of binding to the same epitope as monoclonal antibody J415, for example, which is accordingly capable of competing for binding to PSMA with the monoclonal antibody. As evidenced by the teachings of Greenspan (cited supra), for example, the skilled artisan cannot readily determine if an antibody binds to the same epitope as another antibody without first determining the epitopes to which both antibodies bind. Moreover, Greenspan teaches the determination and characterization of the epitope to which an antibody binds is not routine or conventional and would require undue and unreasonable experimentation.

One could potentially eliminate some antibodies that bind discrete epitopes of PSMA, which are distinct from that to which any of the recited monoclonal antibodies bind, such as monoclonal antibody J591, because, depending upon the conditions under which the assay is performed, these antibodies might not compete as effectively as others for binding to PSMA. However, it is not possible to identify using such competition binding assays antibodies that bind

to the *same epitope* of an antigen. Again, the epitope to which any antibody binds can only be determined empirically using very complex methodology, such as crystallography, mutagenesis, and/or very sensitive binding assays, and arduous analyses of the resulting data.

Therefore, because the artisan cannot predict whether two competing antibodies bind to the same epitope, or different but overlapping epitopes, the epitope binding specificity of an antibody can only be determined empirically. As such, to any extent that the claims are directed to an antibody or antigen binding fragment thereof that binds to the same epitope as any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively, the specification would not provide sufficiently enabling disclosure of the claimed invention, which could only be made, and then used, by performing undue and/or unreasonable experimentation.

Although the prior art enables one to make and use many antibodies, which under certain conditions, could demonstrably "compete" for binding to PSMA with any of monoclonal antibodies J591, J533, E99, and J415 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, Applicant is reminded that to satisfy the enablement requirement, reasonable correlation must exist between the scope of the claims and scope of enablement set forth in the specification. Furthermore, although a specification need not, and preferably omits teachings well known in the prior art, in deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997). Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify antibodies and antigen-binding fragments thereof, which under certain, albeit unspecified assay conditions "compete" for binding to PSMA with any member of the recited pluralities of monoclonal antibodies; yet, defining a substance by its principal

biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

Therefore, in conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. The rejection of claims 144, 156-161, 164, 171-173, 178-204, and 206-218 under 35 U.S.C. 102(e), as being anticipated by U.S. Patent No. 6,962,981 B1, as evidenced by Liu et al. (*Cancer Res.* 1998 Sep 15; **58**: 4055-4060) and George et al. (*Circulation.* 1998; **97**: 900-906), is maintained.

At page 27 of the amendment filed October 11, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Here, the rejected claims are directed to an antibody or antigen binding fragment thereof that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively.

U.S. Patent No. 6,962,981 B1 (Murphy et al.) teaches monoclonal antibodies and antigen binding fragments thereof that bind specifically to the extracellular domain of PSMA; see entire document (e.g., the abstract; Figure 20; column 27, Table 2). Murphy et al. teaches hybridomas producing the disclosed monoclonal antibodies; see, e.g., columns 29 and 30. Murphy et al. teaches the fragments of the disclosed monoclonal antibodies are Fab fragments, F(ab')2) fragments, and Fv fragments; see, e.g., column 14, lines 8-17. Murphy et al. teaches the disclosed monoclonal antibodies or antigen binding fragments thereof are conjugated (bound) to a cytotoxic drug, namely radioisotopes, chemotherapeutic drugs, and toxins; see, e.g., column 14, lines 37-52. Murphy et al. teaches the antibodies or antigen binding fragments thereof are conjugated to beta-emitters (i.e., positron emitting isotopes); see, e.g., column 14, lines 25-36. Murphy et al. teaches the antibodies or antigen binding fragments thereof are conjugated to streptavidin[5] and other biological proteins, which are used as therapeutic agents; see, e.g., column 15, lines 10-30. Murphy et al. teaches the antibodies or antigen binding fragments thereof are labeled with any of a variety of "reporter" substances, including, for example, radioactive isotopes and fluorogenic compounds; see, e.g., column 14, lines 26-36. Murphy et al. teaches isolated clones producing the disclosed antibodies, which are derived from primary hybridomas (i.e., "lymphocytic[6] cell lines"); see, e.g., column 21, lines 35-65. Murphy et al. teaches compositions comprising the antibodies or antigen binding fragments thereof, which are suitably used in a variety of applications, including immunohistological and

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[5] Notably, streptavidin is a biological protein of bacterial origin. Murphy et al. teaches antibodies conjugated to streptavidin and bound to a biotinylated cytotoxin are used therapeutically; see, e.g., column 15, lines 26-30.

[6] The term "lymphocytic" is defined by The On-line Medical Dictionary (available on the Internet at http://cancerweb.ncl.ac.uk/omd/), for example, as meaning: "Pertaining to, characterised by or of the nature of lymphocytes" (© Copyright1997-2005 - The CancerWEB Project). The hybridomas disclosed by Murphy et al. are fusions of B lymphocytes and myeloma cell lines (see, e.g., column 7, line 13, through column 8, line 65. Accordingly, the disclosed clones producing the disclosed monoclonal antibodies, which were derived from primary hybridomas, are deemed the same as the claimed cells derived from "lymphocytic cell lines".

immunocytochemical applications, and diagnostic and therapeutic applications; see, e.g., column 11, line 26, through column 15, line 30. Accordingly, such compositions, particularly those used in therapeutic compositions, are necessarily further comprised of pharmaceutically acceptable carriers, excipients, and/or stabilizers. Murphy et al. teaches kits for use, for example, in diagnosing prostate cancer, which comprise such compositions comprising the disclosed antibodies or antigen binding fragments thereof; see, e.g., column 15, lines 31-43.

Although Murphy et al. does not expressly teach any of the disclosed antibodies or antigen binding fragments thereof "compete" for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99, because the disclosed antibodies bind the extracellular domain of PSMA, there is a reasonable presumption that the antibodies do so. As evidenced by George et al. (cited *supra*), an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody. Thus, at a high enough concentration, or under certain conditions, *any* antibody, but perhaps especially another antibody that binds the same antigen, or more particularly the same epitope recognized by another antibody or an overlapping epitope of the antigen, is expected to "compete" for binding to the antigen with the other antibody. As thoroughly explained above in the rejections of claims under 35 U.S.C. § 112, first and second paragraphs, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what conditions. Therefore, absent a showing of any difference, the antibodies and antigen binding fragments disclosed by Murphy et al. are deemed the same as the claimed antibodies and antigen binding fragments thereof.

Notably, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the antibodies and antigen binding fragments thereof. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the antibodies and antigen binding fragments thereof are different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and

Ex parte Gray, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Furthermore, although Murphy et al. does not expressly teach any of the disclosed antibodies is internalized with PSMA, as evidenced by Liu et al., each of monoclonal antibodies J591, J415, J533, and E99 are internalized with PSMA by LNCaP cells (see entire document; e.g., page 4056, column 1). Accordingly, there is a reasonable presumption that the antibodies disclosed by Murphy et al., which bind to the extracellular domain of PSMA, are internalized with the antigen, particularly since the disclosed antibodies bind the same antigen.

At page 27 of the amendment, Applicant has argued that the declaration under 37 C.F.R. § 1.131 by Neil H. Bander provides evidence of conception and reduction to practice by Applicant of the claimed invention in the United States prior to March 25, 1996, such that U.S. Patent No. 6,962,981 B1 is not prior art. This declaration was filed during prosecution of copending application No. 09/357,704, and a copy of the declaration has been provided, which has been placed in the record.

The merit of the declaration by Dr. Bander has been carefully considered but not found sufficient to antedate the applied reference.

37 C.F.R. § 1.131(b) states:

> The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application.

The declaration by Dr. Bander provides evidence that Applicant had possession of the monoclonal antibodies E99, J533, J415, and J591 prior to March 25, 1999; however, the claims are directed to a genus of antibodies that bind to PSMA and compete for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibodies E99, J533, J415, and J591. Accordingly, the scope of the showing is not commensurate in scope with the breadth of claims. Moreover, as explained in further detail in the paragraphs below, the evidence neither establishes reduction to practice of the claimed invention, nor its conception.

Essentially for the same reasons that the claims have been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling

disclosure, it is submitted that the showing by the declaration is insufficient to establish reduction to practice prior to the effective date of the reference, or to establish conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application.

M.P.E.P. § 715.02 states:

> Even if applicant's 37 CFR 1.131 affidavit is not fully commensurate with the rejected claim, the applicant can still overcome the rejection by showing that the differences between the claimed invention and the showing under 37 CFR 1.131 would have been obvious to one of ordinary skill in the art, in view of applicant's 37 CFR 1.131 evidence, prior to the effective date of the reference(s) or the activity. Such evidence is sufficient because applicant's possession of what is shown carries with it possession of variations and adaptations which would have been obvious, at the same time, to one of ordinary skill in the art. **However, the affidavit or declaration showing must still establish possession of the invention (i.e., the basic inventive concept)** [emboldened for emphasis] and not just of what one reference (in a combination of applied references) happens to show, if that reference does not itself teach the basic inventive concept. *In re Spiller*, 500 F.2d 1170, 182 USPQ 614 (CCPA 1974).

Again, the breadth of the showing by the declaration is not commensurate with the scope of the claims, which are more broadly directed to any of a genus of antibodies that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of monoclonal antibodies E99, J533, J415, and J591.

M.P.E.P. § 715.02 states:

> Where generic claims have been rejected on a reference or activity which discloses a species not antedated by the affidavit or declaration, the rejection will not ordinarily be withdrawn, subject to the rules set forth below, unless the applicant is able to establish that he or she was in possession of the generic invention prior to the effective date of the reference or activity.

There appears no disclosure by the declaration of any factual evidence that Applicant contemplated the generic concept of the invention. Although the declaration discloses antibodies other than monoclonal antibodies E99, J533, J415, and J591, it does not disclose which, if any, compete for binding with PSMA with any one of monoclonal antibodies E99, J533, J415, and J591, and there appears no express reference in any of the evidentiary documents to any antibody that is capable of competing for binding to PSMA with any of these four antibodies.

Furthermore, because the declaration discloses a relatively larger plurality of monoclonal antibodies, which were produced by Applicant, and not just the plurality of the four monoclonal antibodies to which the claims are specifically directed, why then would the differences between

the claimed invention and the showing under 37 C.F.R. § 1.131 have been obvious to one of ordinary skill in the art, in view of the declaratory evidence? Why would the artisan of ordinary skill have selected only antibodies that compete for binding to PSMA with any one of monoclonal antibodies E99, J533, J415, and J591, but not antibodies competing with any of the others? The reason is not immediately apparent; and Applicant has not offered any explanation as to why the declaratory evidence would make obvious any antibody that binds to PSMA and competes for binding to PSMA with any one of the particular monoclonal antibodies to which the claims are directed, but not any of the others.

But for whatever reason, the claims are directed to only antibodies that compete for binding to monoclonal antibodies E99, J533, J415, and J591. The declaratory evidence establishes Applicant's reduction to practice, prior to the date of the reference, of only those monoclonal antibodies; it does not establish a reduction to practice of any antibody that competes for binding to PSMA with any one of these particular four monoclonal antibodies. Moreover, even were the evidence arguably deemed to establish Applicant's possession of the generic concept of the invention, it does not establish Applicant's prior possession of the *particular* species of antibodies, which are disclosed by the reference. The reference describes with particularity 35 antibodies that bind to PSMA; see, e.g., Table 2, which lists 32 of these antibodies, including a large number that bind to the extracellular domain of PSMA (i.e., amino acids 44-750 of the amino acid sequence of the full-length protein, as disclosed therein).

M.P.E.P. § 2131.02 states:

> "A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Absent a showing of any difference, it is submitted that the reference discloses a species of antibody falling within the claimed genus of antibodies that bind to PSMA and compete for binding to PSMA with any one of monoclonal antibodies E99, J533, J415, and J591. As explained in the preceding Office action, this position is considered reasonable.

The declaration shows no objective evidence supporting any assertion that Applicant had reduced to practice any of the particular embodiments of the claimed invention that are disclosed by the reference.

M.P.E.P. § 715.03 states:

> [A] reference or activity which discloses several species of a claimed genus can be overcome directly under 37 CFR 1.131 only by a showing that the applicant completed, prior to the date of the reference or activity, all of the species shown in the reference. *In re Stempel*, 241 F.2d 755, 113 USPQ 77 (CCPA 1957).
>
> Proof of prior completion of a species different from the species of the reference or activity will be sufficient to overcome a reference indirectly under 37 CFR 1.131 *if the species shown in the reference or activity would have been obvious in view of the species shown to have been made by the applicant* [italicized for emphasis]. *In re Clarke*, 356 F.2d 987, 148 USPQ 665 (CCPA 1966); *In re Plumb*, 470 F.2d 1403, 176 USPQ 323 (CCPA 1973); *In re Hostettler*, 356 F.2d 562, 148 USPQ 514 (CCPA 1966).

There appears no reason why any one of the antibodies shown by the reference, which is deemed indistinguishable from the claimed antibody, would have been obvious in view of the showing under 37 C.F.R. § 1.131.

Even if the declaratory evidence arguably shows that Applicant contemplated a genus of antibodies that bind to PSMA and compete for binding to PSMA with any one of monoclonal antibodies E99, J533, J415, and J591, the mere contemplation of such a genus does not provide factual evidence of the conception of the species disclosed by the reference; and conception of the invention prior to the effective date of the reference is not sufficient, unless coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application.

However, diligence need not be considered unless conception of the invention prior to the effective date is clearly established, since diligence comes into question only after prior conception is established. See *Ex parte Kantor*, 177 USPQ 455 (Bd. App. 1958); MPEP § 715.07(a).

Even so, it appears that the declaration provides no showing of due diligence before the date of the prior art publication to a subsequent reduction to practice of genus, nor of each of species disclosed by the reference.

Finally, because the rejected claims have also been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure, the effective filing date of rejected claims is deemed the filing date of the instant application, namely July 20, 1999.

As explained, to receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the declaration by Dr. Bander is insufficient to antedate U.S. Patent No. 6,962,981 B1 (Murphy et al.), which for these reasons is still properly considered prior art under 35 U.S.C. § 102(e).

16. The rejection of claims 144, 156-158, 172, 173, 178, 180, 186, 187, 194, 195, 211, and 213-215 under 35 U.S.C. 102(b), as being anticipated by Liu et al. (Cancer Res. 1997 Sep 1; **57**: 3629-3634) (of record; cited by Applicant), as evidenced by Liu et al. (*Cancer Res.* 1998 Sep 15; **58**: 4055-4060) (of record; cited by Applicant), is maintained.

At page 27 of the amendment filed October 11, 2007, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Here, the rejected claims are directed to an antibody that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively.

Liu et al. teaches monoclonal antibodies 7E11, J591, J533, J415, and E99; see entire document (e.g., page 3631, Figure 3). Liu et al. teaches the antibodies bind to PSMA;

monoclonal antibody 7E11 binds the intracellular domain, whereas monoclonal antibodies J591, J533, J415, and E99 bind the extracellular domain (see, e.g., the abstract). Liu et al. teaches hybridomas producing the disclosed monoclonal antibodies; see, e.g., page 3629, column 2. Liu et al. teaches compositions comprising the disclosed antibodies and, absent a showing otherwise, pharmaceutically acceptable carriers or excipients; see, e.g., page 3629, column 1, through page 3631, column 1. Liu et al. teaches each of monoclonal antibodies J591, J533, and E99 "competed" for binding to PSMA with any of the others; see, e.g., column 3632, column 2. Liu et al. teaches monoclonal antibody J415 competed only with itself; see column 3632, column 2. Liu et al. teaches the disclosed antibodies are bound by a label (i.e., bound to a fluorescently labeled secondary antibody); see, e.g., page 3630, column 2; and page 3631, Figure 3. Liu et al. teaches the antibodies are bound by other detectable labels (i.e., peroxidase- and gold-conjugated secondary antibodies); see, e.g., page 3629, column 1; and page 3630, column 2). Liu et al. teaches the antibodies were labeled by biotinylation, which enabled their detection and quantification; see, e.g., page 3630, column 2; and page 3633, Figure 5.

Although Liu et al. does not expressly teach any of the disclosed antibodies is internalized with PSMA, as evidenced by Liu et al. (1998), each of monoclonal antibodies J591, J415, J533, and E99 are internalized with PSMA by LNCaP cells (see entire document; e.g., page 4056, column 1).

In further response to Applicant's remarks, the rejected claims have also been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure; therefore, the effective filing date of rejected claims is deemed the filing date of the instant application, namely July 20, 1999. As explained above, to receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

17. The rejection of claims 144, 156, 158, 172, 173, 180, 186, 187, 194, 195, 211, 213, and 215 under 35 U.S.C. 102(b), as being anticipated by Israeli et al. (*Cancer Res.* 1994 Apr 1; **54** (7): 1807-1811) (of record; cited by Applicant), as evidenced by George et al. (*Circulation.* 1998; **97**: 900-906), is maintained.

Beginning at page 27 of the amendment filed October 11, 2007, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Here, the rejected claims are directed to an antibody that binds to PSMA and competes for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively.

Israeli et al. teaches monoclonal antibody 7E11; see entire document (e.g., abstract). Israeli et al. teaches the antibody bind to PSMA; see, e.g., the abstract. Israeli et al. teaches compositions comprising the disclosed antibody and, absent a showing otherwise, pharmaceutically acceptable carriers or excipients, such as, e.g., a buffered saline solution; see, e.g., page 1807, column 2, through page 1808, column 1. Liu et al. teaches the disclosed antibody is bound by a label (i.e., bound to a radioactively labeled secondary antibody); see, e.g., page 1808, column 1; and page 1809, Figure 3.

Although Israeli et al. does not expressly teach the disclosed antibody "competes" for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99, as evidenced by George et al. (cited *supra*), an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody. Thus, at a high enough concentration, or under certain conditions, *any* antibody, including an antibody that binds to a different epitope of an antigen than the epitope recognized by another antibody that binds the antigen is expected to "compete" for binding to the antigen with the other antibody. Furthermore, although the specification teaches the antibody disclosed by Israeli et al. (monoclonal antibody 7E11) does not "compete" for binding to PSMA with any of monoclonal antibodies J591, J415, J533, and E99, neither the claims nor the disclosure delineate the

conditions under which such a determination was made. Moreover, as thoroughly explained above in the rejections of claims under 35 U.S.C. § 112, first and second paragraphs, the claims do not define the extent to which the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what conditions. Nevertheless, under certain conditions, monoclonal antibody 7E11 is expected to "compete" to some measurable extent for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99. Therefore, absent a showing of any difference, the antibody disclosed by Israeli et al. is deemed the same as the claimed antibodies and antigen binding fragments thereof.

Again, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the antibodies and antigen binding fragments thereof. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the antibody disclosed by the prior art differs from the claimed antibody. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

18. The rejection of claims 144, 156-161, 167, 170-173, 177, 178, 180, 184-203, 209, 210, and 211-217 under 35 U.S.C. 102(b), as being anticipated by U.S. Patent No. 5,538,866 A, as evidenced by George et al. (*Circulation.* 1998; **97**: 900-906), is maintained.

Beginning at page 28 of the amendment filed October 11, 2007, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Here, the rejected claims are directed to a polyclonal or monoclonal antibody, which competes for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533, and J591 produced by hybridomas deposited under ATCC deposit accession numbers HB-12126, HB-12127, HB-12101, and HB-12109, respectively.

U.S. Patent No. 5,538,866 A (Israeli et al.) teaches polyclonal and monoclonal antibodies that bind specifically to PSMA; see entire document (e.g., column 6, lines 44-47). Israeli et al. teaches the antibody binds the extracellular domain of the antigen, so as to be capable of binding to the surface of prostate cancer cells expressing the antigen; see, e.g., column 13, lines 10-18. Israeli et al. teaches the antibody is conjugated to a cytotoxic drug, namely a radioisotope or biological toxin, such as endotoxin or ricin, which are proteins of bacterial and plant origins, respectively; see, e.g., column 13, lines 5-9; and column 23, lines 44-52. Notably, radioisotopes are detectable labels. Israeli et al. teaches the antibody is conjugated to $Indium^{111}$, a gamma ray emitter; see, e.g., column 13, lines 17 and 18. Israeli et al. teaches a composition comprising the antibody and a pharmaceutically acceptable carrier, excipient, or stabilizer; see, e.g., column 13, lines 22-24. Israeli et al. teaches hybridomas producing the disclosed antibodies; see, e.g., column 12, lines 55-60.

In response to Applicant's argument that U.S. Patent No. 5,538,866 A (Israeli et al.) is not prior art under § 102(b), the rejected claims have also been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure; therefore, the effective filing date of rejected claims is deemed the filing date of the instant application, namely July 20, 1999. U.S. Patent No. 5,538,866 A issued July 23, 1996.

In response to applicant's argument that Israeli et al. fails to anticipate the claimed invention, although Israeli et al. does not expressly teach the disclosed antibody "competes" for binding to PSMA with monoclonal antibodies J591, J415, J533, and/or E99, as evidenced by George et al. (cited *supra*), an antibody need not bind to the same epitope of an antigen as another antibody to measurably "compete" for binding to the antigen with the other antibody. Thus, at a high enough concentration, or under certain conditions, *any* antibody, including an antibody that binds to a different epitope of an antigen than the epitope recognized by another antibody that binds the antigen is expected to "compete" for binding to the antigen with the other antibody.

Neither the claims nor the disclosure delineate the conditions under which such a determination was made. Moreover, as thoroughly explained above in the rejections of claims under 35 U.S.C. § 112, first and second paragraphs, the claims do not define the extent to which

the claimed antibody or antigen binding fragment "competes", nor do they define the methodology by which such a determination is made, and under what conditions.

Nevertheless, the antibodies disclosed by the prior art are **polyclonal**; polyclonal antibodies raised against PSMA bind a plurality of epitopes of PSMA, and are reasonably expected to comprise one or more species of antibody that bind to the same epitopes as monoclonal antibodies J591, J415, J533, and/or E99 and thereby "compete" for binding to PSMA with one or more of the monoclonal antibodies. In addition, because the disclosed antibodies bind the extracellular domain of PSMA, there is a reasonable presumption that the disclosed monoclonal antibodies also "compete" for binding to PSMA with one or more of the recited monoclonal antibodies, especially since, under certain conditions, any monoclonal antibody that binds to PSMA is expected to "compete" to some measurable extent for binding to PSMA with one or more of those antibodies. Therefore, absent a showing of any difference, the polyclonal or monoclonal antibodies disclosed by Israeli et al. are deemed the same as the claimed antibodies and antigen binding fragments thereof.

Again, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the antibodies and antigen binding fragments thereof. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the antibody disclosed by the prior art differs from the claimed antibody. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Beginning at page 29 of the amendment filed October 11, 2007, Applicant has referenced Holmes (*Expert Opin. Investig. Drugs.* 2001 Mar; **10** (3): 511-519), arguing that polyclonal antibodies produced using an immunogen comprised of one of three particular peptide fragments of PSMA and a carrier protein (i.e., KLH) did not bind to intact PSMA.

In response to this argument, the polyclonal antibodies disclosed by the prior art are *not* limited to antibodies produced using the particular immunogen described by Holmes. Israeli et al. describes the polyclonal and monoclonal antibodies as including, but not limited to those directed to a peptide of the PSM antigen selected from Asp-Glu-Leu-Lys-Ala-Glu (SEQ ID No.

35), Asn-Glu-Asp-Gly-Asn-Glu (SEQ ID No. 36), and Lys-Ser-Pro-Asp-Glu-Gly (SEQ ID No. 37); see, e.g., column 6, lines 48-52. Notably, in addition to these three peptide sequences, Israeli discloses the amino acid sequences of at least 9 other peptides, which are fragments of the full-length antigen; see, e.g., columns 16 and 17; and SEQ ID NOs: 3-12, 31, and 34-38. Moreover, Israeli et al. describes the antibodies as inclusive of antibodies produced using the purified, intact antigen; see, e.g., column 6, lines 38-47.

In addition, despite the anecdotal disclosure by Holmes of a peptide that is incapable of eliciting the production of an antibody that binds to the intact protein, it is aptly noted that it was well within the knowledge and skill of the artisan at the time of the invention, and at the time of the disclosure by the prior art, to produce an antibody that binds to an intact antigen using either the intact antigen or only a fragment of the antigen. For example, given the disclosure by the prior art, it would have been immediately appreciated that such polyclonal antibodies could readily be generated using the intact PSM antigen as an immunogen, or perhaps just a substantial portion thereof, such as the extracellular domain of the antigen[7]. Alternatively, as evidenced by Shinnick et al. (*J. Invest. Dermatol.* 1984 Jul; **83** (1 Suppl.): 112s-115s), the skilled artisan could have, as a matter of routine and conventional experimentation, produced a synthetic peptide for use as an immunogen to elicit antibodies that can react with the full-length protein containing that peptide, where such antibodies are directed against a specific region of the protein containing that peptide, which is chosen in advance by the investigator to produce an antibody having a predetermined specificity; see entire document (e.g., the abstract)[8].

Beginning at page 30 of the amendment Applicant has argued that the antibodies of the prior art are "at best described as a genus of antibodies that bind PSMA, and as such they do not anticipate the species of antibodies of the claimed methods" (paragraph 2).

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[7] Notably, Israeli et al. discloses, "generation of polyclonal and monoclonal antibodies against highly antigenic peptide domains of the PSM antigen" is presently underway; see, e.g., column 3, lines 13-22.

[8] In addition, as Applicant has noted, Holmes (*supra*) discloses that the use of slightly longer peptides, as described by Murphy et al. (reference #19), might overcome the problem with using amino acids 63-68, 132-137, or 482-487 as an immunogen to produce antibodies reactive against the intact antigen; see page 513, column 1. Notably, suggesting that doing so is but a matter of routine experimentation, Holmes further discloses that Murphy et al. describes the production of the monoclonal antibody 3F5.4G6, which reacts with the extracellular domain of the intact antigen; this antibody was produced by immunizing mice with a peptide consisting of amino acids 716-723 of PSMA.

In reply, the claims are not directed to any one species of antibody, but are *generic*. Moreover, the claims are directed to a genus of antibodies that bind to PSMA, albeit a genus that is limited to antibodies that compete for binding to PSMA with a monoclonal antibody selected from the monoclonal antibodies of which Applicant was in possession at the time the application was filed (i.e., one of monoclonal antibodies J591, J415, J533, and E99). Similarly, the antibodies described by the prior art are antibodies that bind to PSMA. More particularly, the antibodies described by the prior art are antibodies that bind to the extracellular domain of PSMA, as opposed to any antibody that binds any domain of PSMA, which under some undefined conditions, is capable of competing for binding to PSMA with one of Applicant's four monoclonal antibodies. The antibodies described by the prior art are thus in a sense more limited than the antibodies to which the claims are directed, since, as explained, under certain conditions, any antibody that binds to PSMA is capable of "competing" with another antibody that binds to this same antigen, such as one of monoclonal antibodies J591, J415, J533, and E99.

In further reply to this line of argument, although the claims are not limited to antibodies that bind to the same epitope or domain of PSMA as any of monoclonal antibodies J591, J415, J533, and E99, each of these monoclonal antibodies binds to the extracellular domain of PSMA, and so do the antibodies disclosed by the prior art. For this reason, it has been submitted that there is a reasonable expectation that at least one of the 30 or more different monoclonal antibodies described by Israeli et al. binds to the same epitope as one or more of Applicant's monoclonal antibodies, and if so, competes for binding to PSMA with those monoclonal antibodies.

The antibodies disclosed by the prior art are either encompassed by the claims, or they are not, i.e., the antibodies described by Israeli either compete for binding to PSMA with one of monoclonal antibodies J591, J415, J533, and E99, or they do not.

The prior art cannot have known that the antibodies disclosed therein bind to the same epitopes as any one of Applicant's *novel* monoclonal antibodies, so it should be of little consequence that the art is silent as to whether or not their antibodies are capable of competing for binding to PSMA with one of monoclonal antibodies J591, J415, J533, and E99. That property of the antibodies of the prior art to do so, or not to do so, is inherent; moreover, it is a

matter of fact that is determinable, but as has been explained previously, the Office does not have the facilities for establishing that there are material, structural and/or functional differences between the products of the prior art and the products that are encompassed by the claims. Thus it is Applicant's burden to prove that the antibody disclosed by the prior art differs from the claimed antibody.

As to inherency, the Court has noted that "[u]nder the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Mehl/Biophile Int'l Corp. v. Miligraum*, 192 F.2d 1362, 1366, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (citations omitted).

In addition, granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. See *In re Baxter Travenol Labs,* 21 USPQ2d 1281 (Fed. Cir. 1991). See also: *In re Wiseman,* 201 USPQ 658 (CCPA 1979); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1575 (Fed. Cir. 1990); and *Bristol-Myers Squibb Company v. Ben Venue Laboratories*, 58 USPQ2d 1508 (CAFC 2001). See M.P.E.P. § 2145.

As such, although Applicant's arguments have been carefully considered, the Office's position is founded in scientific reasoning, factual evidence, and an analysis of legal precedence, and given the fact that Israeli et al. disclosed polyclonal antibodies, as well as at least 30 different monoclonal antibodies that bind to the extracellular domain of PSMA, it is reasonably concluded *in the absence of factual evidence indicating otherwise* that the prior art's disclosure is anticipatory of the claimed invention.

19. The rejection of claims 144, 156-168, 170-204, and 206-218 under 35 U.S.C. 102(e), as being anticipated by U.S. Patent Application Publication No. 2004/0213791 A1 or U.S. Patent Application Publication No. 2004/0120958 A1, is maintained.

Beginning at page 31 of the amendment filed October 11, 2007, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

U.S. Patent Application Publication No. 2004/0213791 A1 (Bander et al.) teaches anti-PSMA antibodies or antigen binding fragments thereof, wherein said antibodies comprise the complementarity determining regions (CDRs) of any of monoclonal antibodies J591, J415, J533 and E99, or hybridomas, or other cell lines producing such antibodies; see entire document (e.g., the abstract; the claims; paragraph [0012]). These antibodies bind to the same epitope(s) as monoclonal antibodies J591, J415, J533 and/or E99 and therefore "compete" for binding to PSMA with any one or more of those monoclonal antibodies.

Furthermore, at paragraph [0014] Bander et al. teaches the anti-PSMA antibody binds all or part of an epitope bound by an antibody described herein, e.g., a J591, E99, J415, and J533 antibody. Bander et al. teaches the anti-PSMA antibody can inhibit, e.g., competitively inhibit, the binding of an antibody described herein, e.g., a J591, E99, J415, and J533 antibody, to human PSMA; and Bander et al. teaches an anti-PSMA antibody may bind to an epitope, e.g., a conformational or a linear epitope, which epitope when bound prevents binding of an antibody described herein, e.g., a J591, E99, J415, and J533 antibody. Bander et al. teaches the epitope can be in close proximity spatially or functionally-associated, e.g., an overlapping or adjacent epitope in linear sequence or conformational space, to the one recognized by the J591, E99, J415, or J533 antibody.

Bander et al. teaches fragments of such antibodies are selected from the group consisting of Fab, $F(ab')_2$, Fv, and single chain Fv fragments; see, e.g., paragraph [0017]. Bander et al. teaches the antibodies or antigen binding fragments are internalized with PSMA; see, e.g., paragraph [0199]. Bander et al. teaches the antibodies or antigen binding fragments thereof are coupled to a cytotoxic moiety selected from a cytotoxic protein of plant, fungal, or bacterial origin, a radioisotope that emits alpha, beta, or gamma radiation, a cytotoxic or therapeutic drug (e.g., a taxane); see, e.g., paragraphs [0145] and [0390]. Bander et al. teaches the antibodies or antigen binding fragments thereof, which are coupled to a label selected from biologically active enzymes, prosthetic groups, luminescent materials, bioluminescent materials, fluorescent materials, paramagnetic materials and radioactive ions; see, e.g., paragraph [0145]. Bander et al. teaches the radioisotopes to which the claimed antibodies or antigen binding fragments are coupled are selected from ^{212}Bi, ^{213}Bi, ^{211}At, ^{186}Re, ^{90}Y, ^{131}I, ^{32}P, ^{125}I, ^{3}H, ^{14}C, ^{188}Rh, and ^{99}mTc;

see, e.g., paragraph [0391]. Bander et al. teaches pharmaceutical compositions comprising the antibodies or antigen binding fragments thereof and a pharmaceutically acceptable carrier, excipient, or stabilizer; see, e.g., paragraph [0147]. Bander et al. teaches kits comprising the disclosed antibodies and antigen binding fragments thereof; see, e.g., paragraphs [0367]-[0371]. Bander et al. teaches the cells producing the antibodies are derived from lymphocytic cell lines; see, e.g., paragraph [0349].

U.S. Patent Application Publication No. 2004/0120958 A1 is a continuation-in-part of the earlier filed application, namely copending Application No. 10/379,838, which is a continuation-in-part of another earlier filed application, which was published as the above cited U.S. Patent Application Publication No. 2004/0213791 A1. Accordingly, absent a showing otherwise, it is submitted that U.S. Patent Application Publication No. 2004/0120958 A1 teaches the subject matter taught by U.S. Patent Application Publication No. 2004/0213791 A, which has been incorporated in its entirety by reference therein, and therefore provides a disclosure that anticipates the inventions of claims 144, 156-168, 170-204, and 206-218.

Applicant's argument that these references are not prior art is noted, but the rejected claims have also been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure; therefore, the effective filing date of rejected claims is deemed the filing date of the instant application, namely July 20, 1999. U.S. Patent No. 5,538,866 A issued July 23, 1996.

20. The provisional rejection of claims 144, 156-168, 170-204, and 206-218 under 35 U.S.C. 102(e), as being anticipated by copending Application No. 10/379,838, which has a common inventor with the instant application, is maintained. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

Notably, copending Application No. 10/379,838 has not been published.

Copending Application No. 10/379,838 is a continuation-in-part of the earlier filed application published as the U.S. Patent Application Publication No. 2004/0213791 A1, which is

cited as the basis of the rejection set forth in section 17 above. Accordingly, absent a showing otherwise, it is submitted that the specification of copending Application No. 10/379,838 teaches the subject matter taught by U.S. Patent Application Publication No. 2004/0213791 A, which has been incorporated in its entirety by reference therein, and therefore provides a disclosure that anticipates the inventions of claims 144, 156-168, and 170-210.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Applicant's argument that this reference is not prior art is noted, but the rejected claims have also been rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and/or a sufficiently enabling disclosure; therefore, the effective filing date of rejected claims is deemed the filing date of the instant application, namely July 20, 1999. U.S. Patent No. 5,538,866 A issued July 23, 1996.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
December 19, 2007